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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,479	12/12/2001	Robert A. Reenan	13407-012001 / 00-066	5194

26161 7590 10/07/2003

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EXAMINER	
KAPUST, RACHEL B	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 10/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,479	REENAN ET AL.	
	Examiner	Art Unit	
	Rachel B. Kapust	1647	

-- Th MAILING DATE of this communication app ars on the cov r sh et with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-84* is/are pending in the application.

4a) Of the above claim(s) *1-29 and 33-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,32,51-81,83 and 84* is/are rejected.

7)☒ Claim(s) *31 and 82* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0402* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group IV in Paper No. 0703 is acknowledged. Claims 1-29 and 33-50 are withdrawn from consideration pursuant to 37 CFR § 1.142(b). Claims 30-32 and 51-84 are under consideration.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on April 4, 2002, March 31, 2003, and July 7, 2003 are mostly in compliance with the provisions of 37 CFR 1.97. The information disclosure statement filed April 4, 2002 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein for Lowman *et al.*, "Selecting High-Affinity Binding Proteins by Monovalent Phage Display" in Biochemistry, Vol. 30, No. 45, p. 10832-10838 (1991) has not been considered because a copy of the reference was not submitted. Other than said reference, the information disclosure statements have been considered by the examiner.

Specification

The disclosure is objected to because of the following informalities: Figure 9 contains amino acid or nucleic acid sequences. On page 45, there are amino acid sequences with no sequence identifiers. Applicants are directed to 37 C.F.R. § 1.821(d)

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

In order to comply with 37 C.F.R. 1.821, appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 61 recites the limitation "the transport activity" in reference to claim 51. Claim 51, however, does not refer to "transport activity." There is insufficient antecedent basis for this limitation in the claim.

Claims 72 and 75-80 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "transporter-related parameter" in claim 72 is a relative term which renders the claim indefinite. The term "transporter-related parameter" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 51-53, 59, 60, 64-71, 83, and 84 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are directed to methods for evaluating the "interaction" of a test molecule with a transporter polypeptide. However, it is not clear whether the claims only embody the interaction between the test molecule and the transporter polypeptide, whether the claims embody interactions between transporter proteins and their binding partners, whether the claims embody interactions between the test molecule and the transporter protein binding partners, whether the claims embody all interactions or if the claims only embody some of these interactions.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30, 32, 51, 52, 54-74, 76-80, and 83 are rejected under 35 U.S.C. 112, first paragraph because the specification does not reasonably provide enablement for proteins that are at least 25% identical to SEQ ID NO: 2, at least 85% identical to SEQ ID NO: 2, or active fragments of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie *et al.* (1990), *Science* 247: 1306-1310, especially p. 1306, column 2, paragraph 2; Wells (1990), *Biochemistry* 29: 8509-8517; Ngo *et al.* (1994), The Protein Folding Problem and Tertiary Structure Prediction, Merz *et al.*, eds., Birkhauser, Boston, pp. 14-16).

However, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein that are tolerant to change and the nature and extent of changes that can be made in these positions. For instance, SEQ ID NO: 2 is a polypeptide consisting of 572 amino acids. Claims 30, 32, 51, 53, 56, 58-59, 61-74, 76-80, and 83 are drawn to methods of screening polypeptides that are at least 25% or 85% identical to SEQ ID NO: 2. These polypeptides could have structures that are very different from that of SEQ ID NO: 2.

Regarding claims 52, 55, 57, and 60, which are drawn to methods of screening proteins comprising an active fragment of SEQ ID NO: 2, the specification provides no guidance as to which (if any) of the amino acids can be changed or deleted to yield a functional equivalent of the INDY protein. Although the specification outlines art-recognized procedures for producing and screening for active protein variants (p. 18-19), this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active site or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Due to the large quantity of experimentation necessary to generate the infinite number of variants recited in the claims and screen the same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

In addition, claims 30, 32, 51, 52, 54-74, 76-80, and 83 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are drawn to a genus, *i.e.* proteins of at least 25% identity to SEQ ID NO: 2 and biologically active fragments. Applicants have disclosed five species, the polypeptides of SEQ ID NOS: 2, 3, 4, 5 and 6, but have not disclosed sufficient species for the broad genus of any protein at least 25% identical to SEQ ID NO: 2 and related biologically active proteins.

The instant disclosure of five species of polypeptides does not adequately describe the scope of the claimed genus, which encompasses hundreds of thousands of different peptides with

varying structures and functions. A description of a genus of polypeptides may be achieved by means of a recitation of a representative number of polypeptides, defined by amino acid sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, said features constituting a substantial portion of the genus. The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed.

Although Applicants list examples of sodium dicarboxylate cotransporters in the specification (see p. 17 and 18), structural features that could distinguish the compounds in the genus, INDY related proteins, from other dicarboxylate cotransporters are missing from the disclosure. For instance, Pajor (*Annu. Rev. Physiol.* (1999), 61: 663-682, submitted by Applicants in IDS) teaches that there are several categories of sodium-coupled dicarboxylate transporters, and the transporters differ in substrate affinity and selectivity, in sensitivity to inhibition by lithium, and in tissue distribution and species distribution (see table on p. 665). Applicants fail to provide examples of structural features that would distinguish an INDY related protein from another sodium-coupled dicarboxylate transporter. Furthermore, the prior art does not provide compensatory structural or correlative teaching sufficient to enable one of skill to isolate and identify the polypeptides encompassed: there is no guidance in the art as to what the defining characteristics of INDY might be. Thus, no identifying characteristics or properties of the instant peptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, the disclosure of SEQ ID NOS: 2, 3, 4, 5, and 6 is insufficient to describe the genus. Therefore, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Claim Rejections - 35 USC § 103

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 81 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sekine *et al.* (1998) *Am. J. Physiol.* 275: F298-F305 (submitted by Applicants in IDS), Pajor (1996), *Am. J. Physiol.* 270: F642-F648, and Chen *et al.* (1999), *J. Clin. Invest.* 103: 1159-1168 and further in view of Amara *et al.*, U.S. Patent No. 6,100,085.

Sekine *et al.* teach the amino acid sequence of a rat renal sodium dicarboxylate transporter (rNaDC-1) which is the same as SEQ ID NO: 4 (see p. F300). Sekine *et al.* teach that rNaDC-1 mediates di- and tricarboxylate transport (p. F305). However, Sekine *et al.* do not teach a method of assessing the inhibitory activity of a test substance on a polypeptide comprising SEQ ID NO: 4.

Chen *et al.* teach the amino acid sequence of a rat sodium-dependent dicarboxylate transporter which is the same as SEQ ID NO: 5 (see p. 1162). However, Chen *et al.* do not teach a method of assessing the inhibitory activity of a test substance on a polypeptide comprising SEQ ID NO: 5.

Pajor teaches the amino acid sequence of a human renal Na(+)-dicarboxylate cotransporter which is the same as SEQ ID NO: 6. However, Pajor does not teach a method of assessing the inhibitory activity of a test substance on a polypeptide comprising SEQ ID NO: 6.

Amara *et al.* teach methods for screening compounds for their ability to inhibit, facilitate or modulate the biochemical activity of transporter molecules, such that cells transformed with a recombinant expression construct are contacted with such a compound, and the effect of the compound on the transport of the appropriate amino acid is assayed (column 6, line 60 through column 7, line 3). It would have been obvious for a person of ordinary skill in the art to use the method as taught by Amara *et al.* to assess the inhibitory activity of a test substance on a polypeptide comprising either SEQ ID NO: 4, 5, or 6. The polypeptides taught by Sekine *et al.*, Chen *et al.*, and Pajor are all dicarboxylate transporters, therefore it would have been obvious to monitor the amount of carboxylate transported in the assay. The motivation to do so can be found in Sekine *et al.*, who teach that sodium-dicarboxylate transporters are associated with urolithiasis (p. F298), and in Chen *et al.*, who teach that citrate functions as an endogenous inhibitor for renal stone formation (p. 1167). Chen *et al.* further teach that maintenance of urine citrate levels "is essential to prevent the precipitation of calcium salts," and changes in dicarboxylate uptake may affect transport of citrate on the luminal side. Accordingly, a person of ordinary skill in the art would want to investigate the results of inhibiting sodium dicarboxylate transporters in relationship to urolithiasis. Thus, the invention taken as a whole is *prima facie* obvious over the prior art.

Allowable Subject Matter

Claims 31 and 82 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 53, 75, and 84 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. § 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel B. Kapust whose telephone number is (703) 305-0634. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RBK